



A434.ST25
SEQUENCE LISTING

43

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Ortwine, Daniel F
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Roark, William H

<120> Matrix Metalloproteinase Inhibitors

<130> A0000434-01-CFP Reg US App

<140> 10/075,069

<141> 2002-02-13

<150> 60/268,821

<151> 2001-02-14

<160> 1

<170> PatentIn version 3.1

<210> 1

<211> 471

<212> PRT

<213> Homo sapiens

<400> 1

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Cys Arg Ala Leu Pro Leu Pro Ser Gly Gly Asp Glu Asp Asp Leu Ser
20 25 30

Glu Glu Asp Leu Gln Phe Ala Glu Arg Tyr Leu Arg Ser Tyr Tyr His
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Pro Thr Asn Leu Ala Gly Ile Leu Lys Glu Asn Ala Ala Ser Ser Met
 50 55 60

Thr Glu Arg Leu Arg Glu Met Gln Ser Phe Phe Gly Leu Glu Val Thr
 65 70 75 80

Gly Lys Leu Asp Asp Asn Thr Leu Asp Val Met Lys Lys Pro Arg Cys
 85 90 95

Gly Val Pro Asp Val Gly Glu Tyr Asn Val Phe Pro Arg Thr Leu Lys
 100 105 110

Trp Ser Lys Met Asn Leu Thr Tyr Arg Ile Val Asn Tyr Thr Pro Asp
 115 120 125

Met Thr His Ser Glu Val Glu Lys Ala Phe Lys Lys Ala Phe Lys Val
 130 135 140

Trp Ser Asp Val Thr Pro Leu Asn Phe Thr Arg Leu His Asp Gly Ile
 145 150 155 160

Ala Asp Ile Met Ile Ser Phe Gly Ile Lys Glu His Gly Asp Phe Tyr
 165 170 175

Pro Phe Asp Gly Pro Ser Gly Leu Leu Ala His Ala Phe Pro Pro Gly
 180 185 190

Pro Asn Tyr Gly Gly Asp Ala His Phe Asp Asp Asp Glu Thr Trp Thr
 195 200 205

Ser Ser Ser Lys Gly Tyr Asn Leu Phe Leu Val Ala Ala His Glu Phe
 210 215 220

Gly His Ser Leu Gly Leu Asp His Ser Lys Asp Pro Gly Ala Leu Met
 225 230 235 240

Phe Pro Ile Tyr Thr Tyr Thr Gly Lys Ser His Phe Met Leu Pro Asp
 245 250 255

Asp Asp Val Gln Gly Ile Gln Ser Leu Tyr Gly Pro Gly Asp Glu Asp
 260 265 270

Pro Asn Pro Lys His Pro Lys Thr Pro Asp Lys Cys Asp Pro Ser Leu
 275 280 285

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Ser Leu Asp Ala Ile Thr Ser Leu Arg Gly Glu Thr Met Ile Phe Lys
290 295 300

Asp Arg Phe Phe Trp Arg Leu His Pro Gln Gln Val Asp Ala Glu Leu
305 310 315 320

Phe Leu Thr Lys Ser Phe Trp Pro Glu Leu Pro Asn Arg Ile Asp Ala
325 330 335

Ala Tyr Glu His Pro Ser His Asp Leu Ile Phe Ile Phe Arg Gly Arg
340 345 350

Lys Phe Trp Ala Leu Asn Gly Tyr Asp Ile Leu Glu Gly Tyr Pro Lys
355 360 365

Lys Ile Ser Glu Leu Gly Leu Pro Lys Glu Val Lys Lys Ile Ser Ala
370 375 380

Ala Val His Phe Glu Asp Thr Gly Lys Thr Leu Leu Phe Ser Gly Asn
385 390 395 400

Gln Val Trp Arg Tyr Asp Asp Thr Asn His Ile Met Asp Lys Asp Tyr
405 410 415

Pro Arg Leu Ile Glu Glu Asp Phe Pro Gly Ile Gly Asp Lys Val Asp
420 425 430

Ala Val Tyr Glu Lys Asn Gly Tyr Ile Tyr Phe Phe Asn Gly Pro Ile
435 440 445

Gln Phe Glu Tyr Ser Ile Trp Ser Asn Arg Ile Val Arg Val Met Pro
450 455 460

Ala Asn Ser Ile Leu Trp Cys
465 470

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FIG. 1

SEQUENCE LISTING

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 20 <212> PRT
 <213> Homo sapiens
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 Cys Arg Ala Leu Pro Leu Pro Ser Gly Gly Asp Glu Asp Asp Leu Ser
 20 25 30
 30 Glu Glu Asp Leu Gln Phe Ala Glu Arg Tyr Leu Arg Ser Tyr Tyr His
 35 40
 Pro Thr Asn Leu Ala Gly Ile Leu Lys Glu Asn Ala Ala Ser Ser Met
 50 55 60
 35 Thr Glu Arg Leu Arg Glu Met Gln Ser Phe Phe Gly Leu Glu Val Thr
 65 70 75 80
 Gly Lys Leu Asp Asp Asn Thr Leu Asp Val Met Lys Lys Pro Arg Cys
 40 85 90 95
 Gly Val Pro Asp Val Gly Glu Tyr Asn Val Phe Pro Arg Thr Leu Lys
 100 105 110
 45 Trp Ser Lys Met Asn Leu Thr Tyr Arg Ile Val Asn Tyr Thr Pro Asp
 115 120 125
 Met Thr His Ser Glu Val Glu Lys Ala Phe Lys Lys Ala Phe Lys Val
 130 135 140
 50 Trp Ser Asp Val Thr Pro Leu Asn Phe Thr Arg Leu His Asp Gly Ile
 145 150 155 160
 Ala Asp Ile Met Ile Ser Phe Gly Ile Lys Glu His Gly Asp Phe Tyr
 165 170 175
 55 Pro Phe Asp Gly Pro Ser Gly Leu Leu Ala His Ala Phe Pro Pro Gly
 180 185 190

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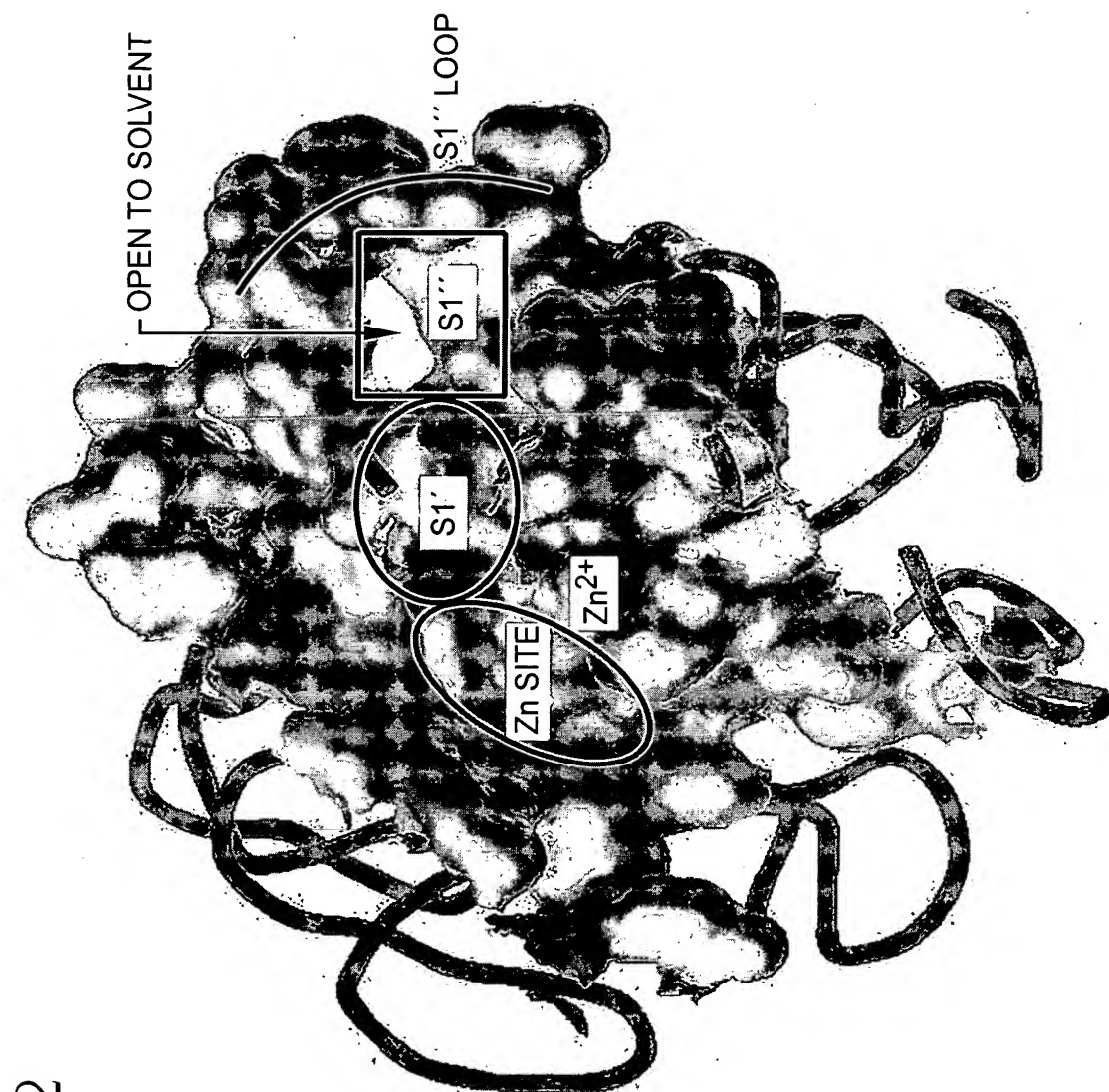
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FIG. 1A

| | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| | Pro | Asn | Tyr | Gly | Gly | Asp | Ala | His | Phe | Asp | Asp | Asp | Glu | Thr | Trp | Thr | |
| | | 195 | | | | | | 200 | | | | | 205 | | | | |
| 5 | Ser | Ser | Ser | Lys | Gly | Tyr | Asn | Leu | Phe | Leu | Val | Ala | Ala | His | Glu | Phe | |
| | | 210 | | | | | 215 | | | | | 220 | | | | | |
| 10 | Gly | His | Ser | Leu | Gly | Leu | Asp | His | Ser | Lys | Asp | Pro | Gly | Ala | Leu | Met | |
| | 225 | | | | | 230 | | | | | 235 | | | | | 240 | |
| | Phe | Pro | Ile | Tyr | Thr | Tyr | Thr | Gly | Lys | Ser | His | Phe | Met | Leu | Pro | Asp | |
| | | | | | 245 | | | | | 250 | | | | | 255 | | |
| 15 | Asp | Asp | Val | Gln | Gly | Ile | Gln | Ser | Leu | Tyr | Gly | Pro | Gly | Asp | Glu | Asp | |
| | | | | 260 | | | | | 265 | | | | | 270 | | | |
| | Pro | Asn | Pro | Lys | His | Pro | Lys | Thr | Pro | Asp | Lys | Cys | Asp | Pro | Ser | Leu | |
| | | | 275 | | | | | 280 | | | | | 285 | | | | |
| 20 | Ser | Leu | Asp | Ala | Ile | Thr | Ser | Leu | Arg | Gly | Glu | Thr | Met | Ile | Phe | Lys | |
| | | 290 | | | | | 295 | | | | | 300 | | | | | |
| 25 | Asp | Arg | Phe | Phe | Trp | Arg | Leu | His | Pro | Gln | Gln | Val | Asp | Ala | Glu | Leu | |
| | 305 | | | | | 310 | | | | | 315 | | | | | 320 | |
| | Phe | Leu | Thr | Lys | Ser | Phe | Trp | Pro | Glu | Leu | Pro | Asn | Arg | Ile | Asp | Ala | |
| | | | | | 325 | | | | | 330 | | | | | 335 | | |
| 30 | Ala | Tyr | Glu | His | Pro | Ser | His | Asp | Leu | Ile | Phe | Ile | Phe | Arg | Gly | Arg | |
| | | | | 340 | | | | | 345 | | | | | 350 | | | |
| | Lys | Phe | Trp | Ala | Leu | Asn | Gly | Tyr | Asp | Ile | Leu | Glu | Gly | Tyr | Pro | Lys | |
| | | | 355 | | | | | 360 | | | | | 365 | | | | |
| 35 | Lys | Ile | Ser | Glu | Leu | Gly | Leu | Pro | Lys | Glu | Val | Lys | Lys | Ile | Ser | Ala | |
| | | 370 | | | | | 375 | | | | | 380 | | | | | |
| 40 | Ala | Val | His | Phe | Glu | Asp | Thr | Gly | Lys | Thr | Leu | Leu | Phe | Ser | Gly | Asn | |
| | 385 | | | | | 390 | | | | | 395 | | | | | 400 | |
| | Gln | Val | Trp | Arg | Tyr | Asp | Asp | Thr | Asn | His | Ile | Met | Asp | Lys | Asp | Tyr | |
| | | | | | 405 | | | | | 410 | | | | | 415 | | |
| 45 | Pro | Arg | Leu | Ile | Glu | Glu | Asp | Phe | Pro | Gly | Ile | Gly | Asp | Lys | Val | Asp | |
| | | | | 420 | | | | | 425 | | | | | 430 | | | |
| 50 | Ala | Val | Tyr | Glu | Lys | Asn | Gly | Tyr | Ile | Tyr | Phe | Phe | Asn | Gly | Pro | Ile | |
| | | | 435 | | | | | 440 | | | | | 445 | | | | |
| | Gln | Phe | Glu | Tyr | Ser | Ile | Trp | Ser | Asn | Arg | Ile | Val | Arg | Val | Met | Pro | |
| | | 450 | | | | | 455 | | | | | 460 | | | | | |
| 55 | Ala | Asn | Ser | Ile | Leu | Trp | Cys | | | | | | | | | | |
| | 465 | | | | | 470 | | | | | | | | | | | |

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FIG. 3 SYNTHESIS EXAMPLE 1 BINDING MODE

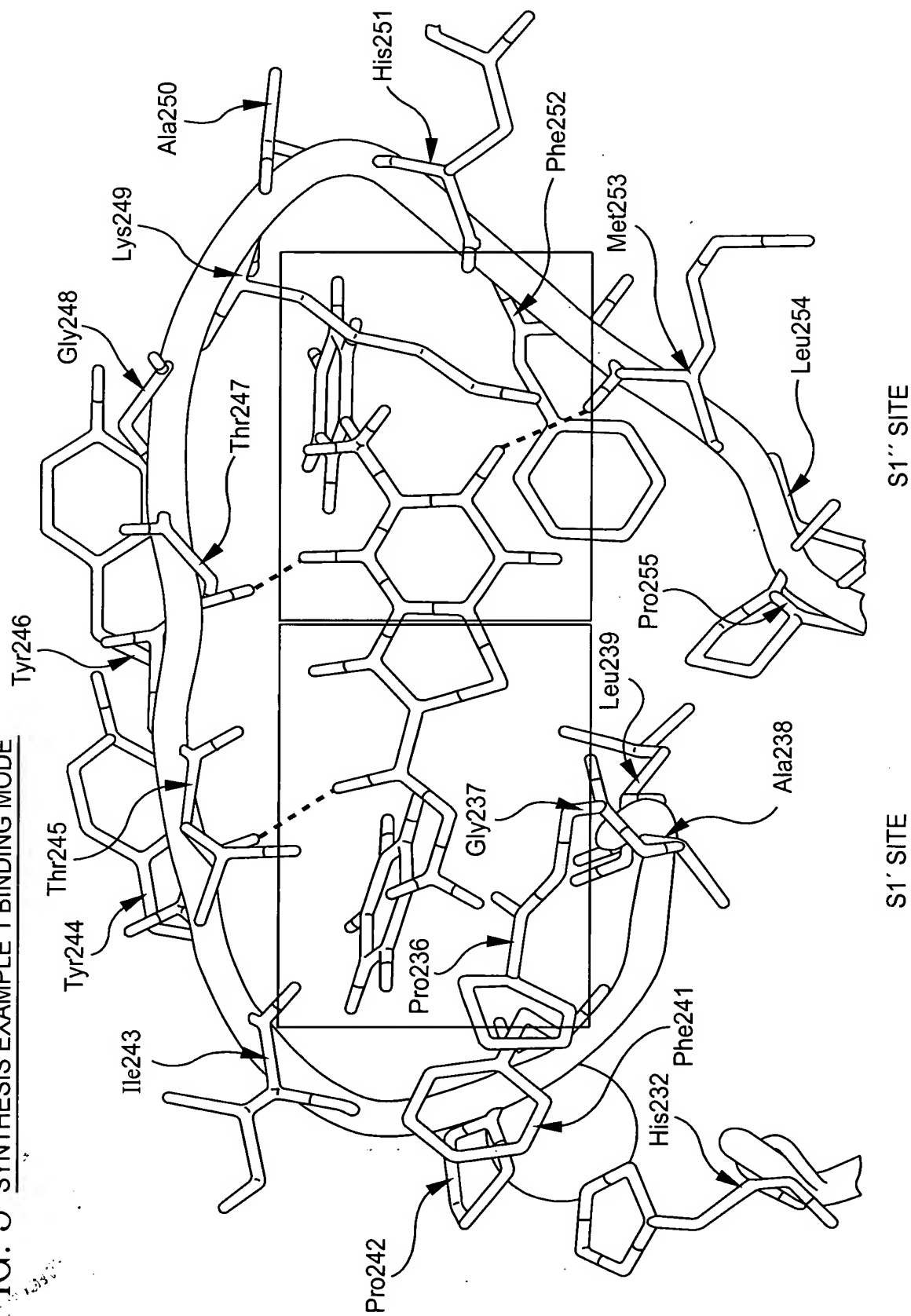
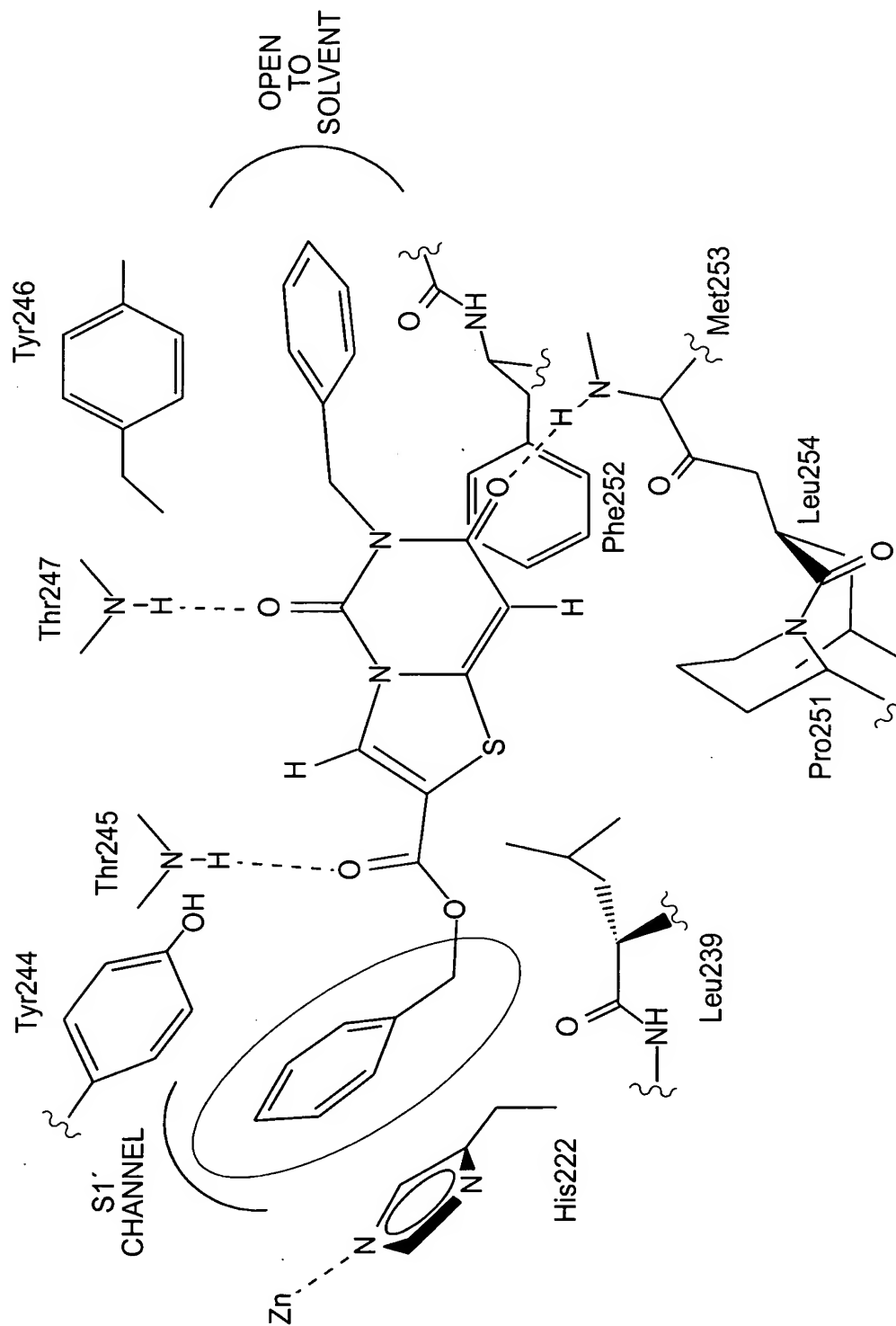
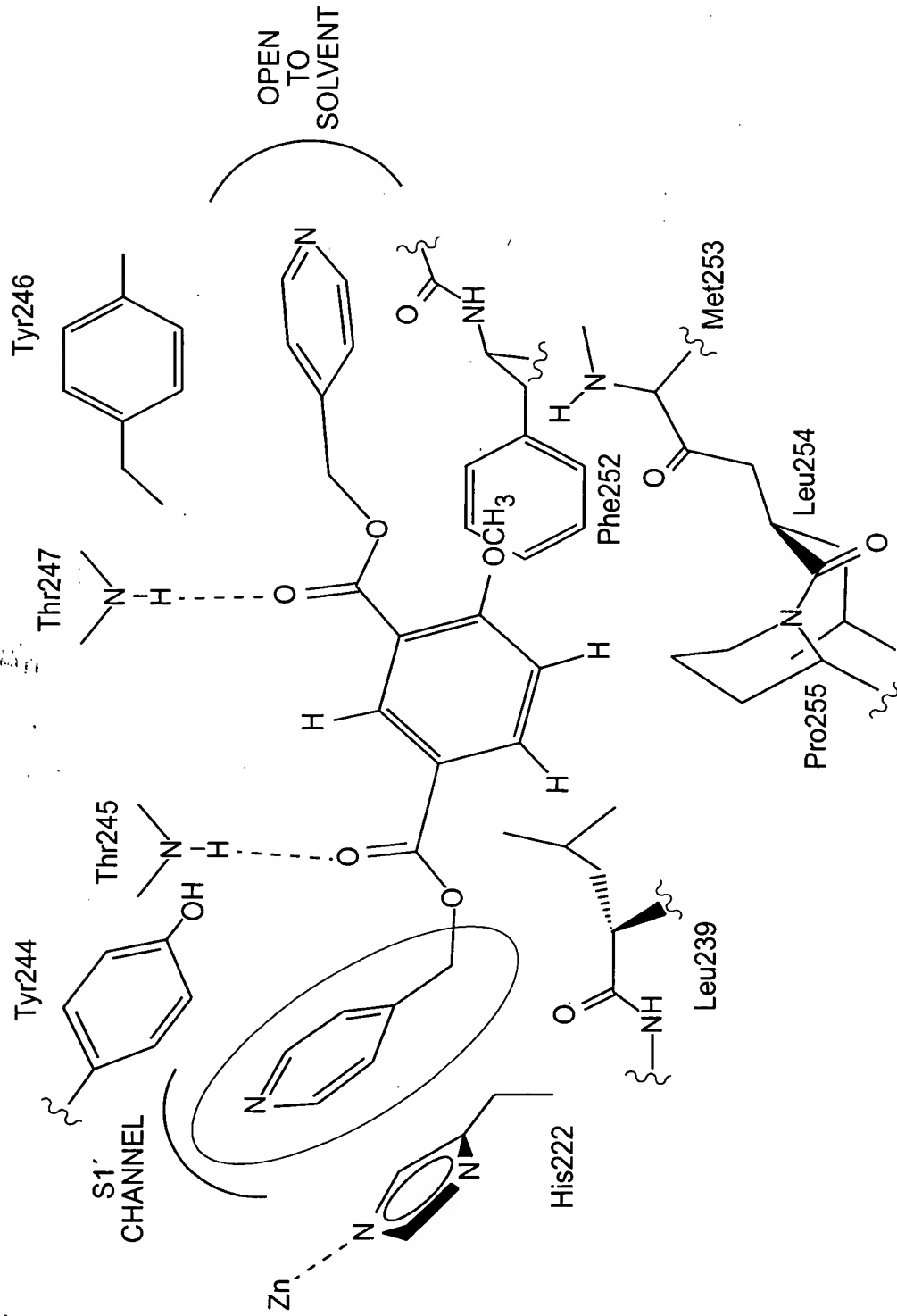


FIG. 4 SYNTHESIS EXAMPLE 1 BINDING MODE

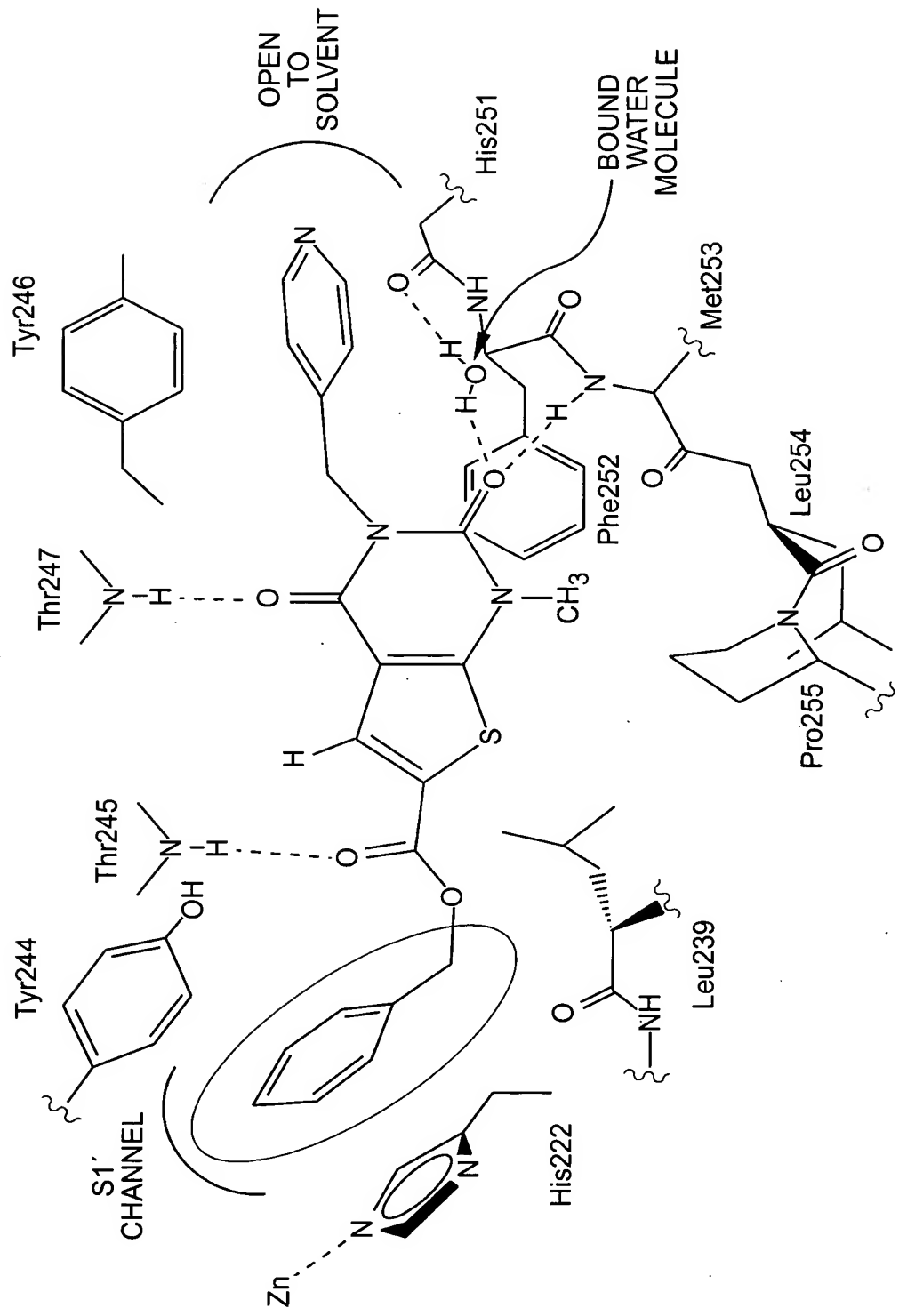


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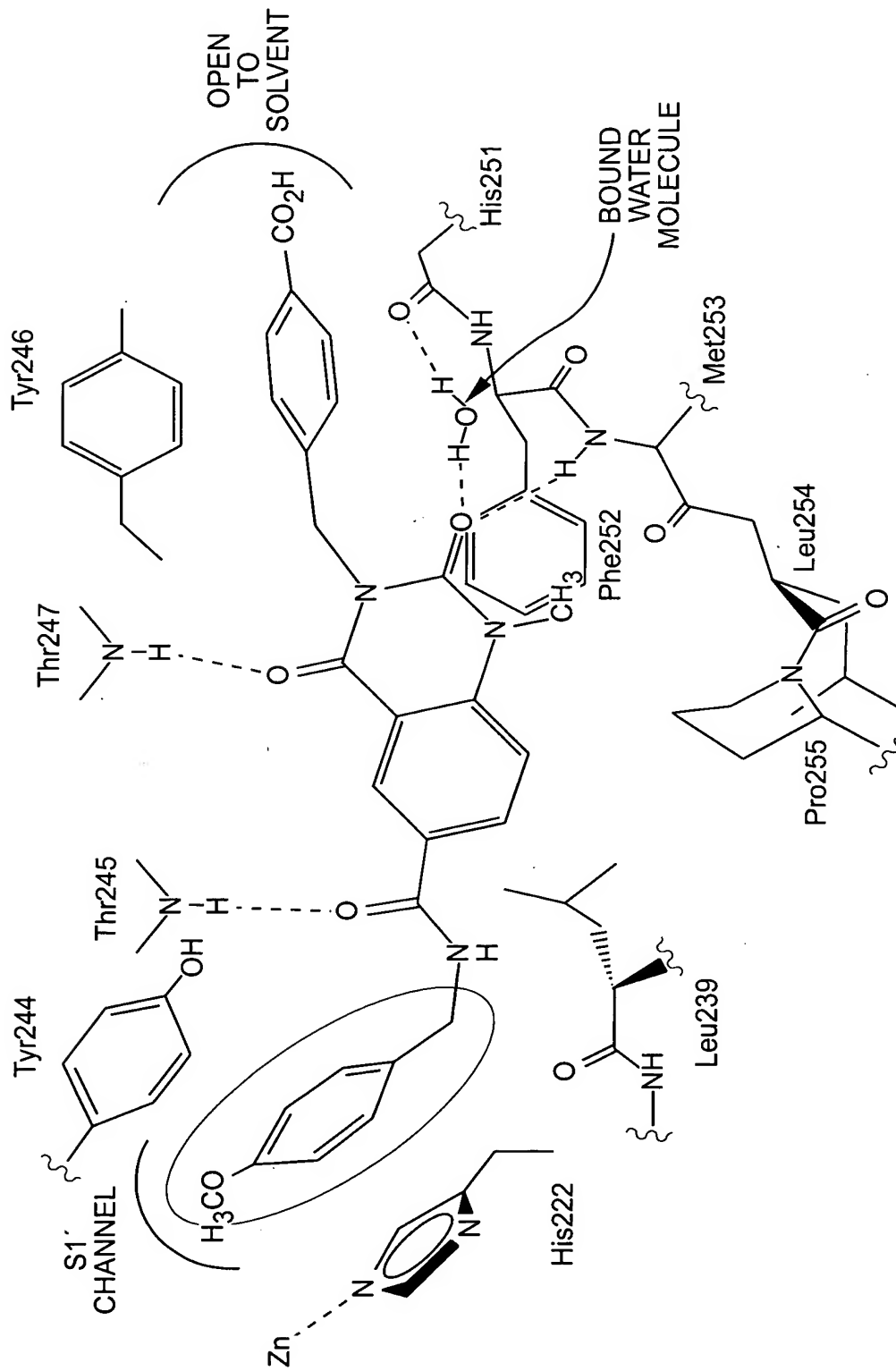
FIG. 5 SYNTHESIS EXAMPLE 10 BINDING MODE

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FIG. 6 FUSED BICYCLIC PYRIMIDONES-BINDING MODE



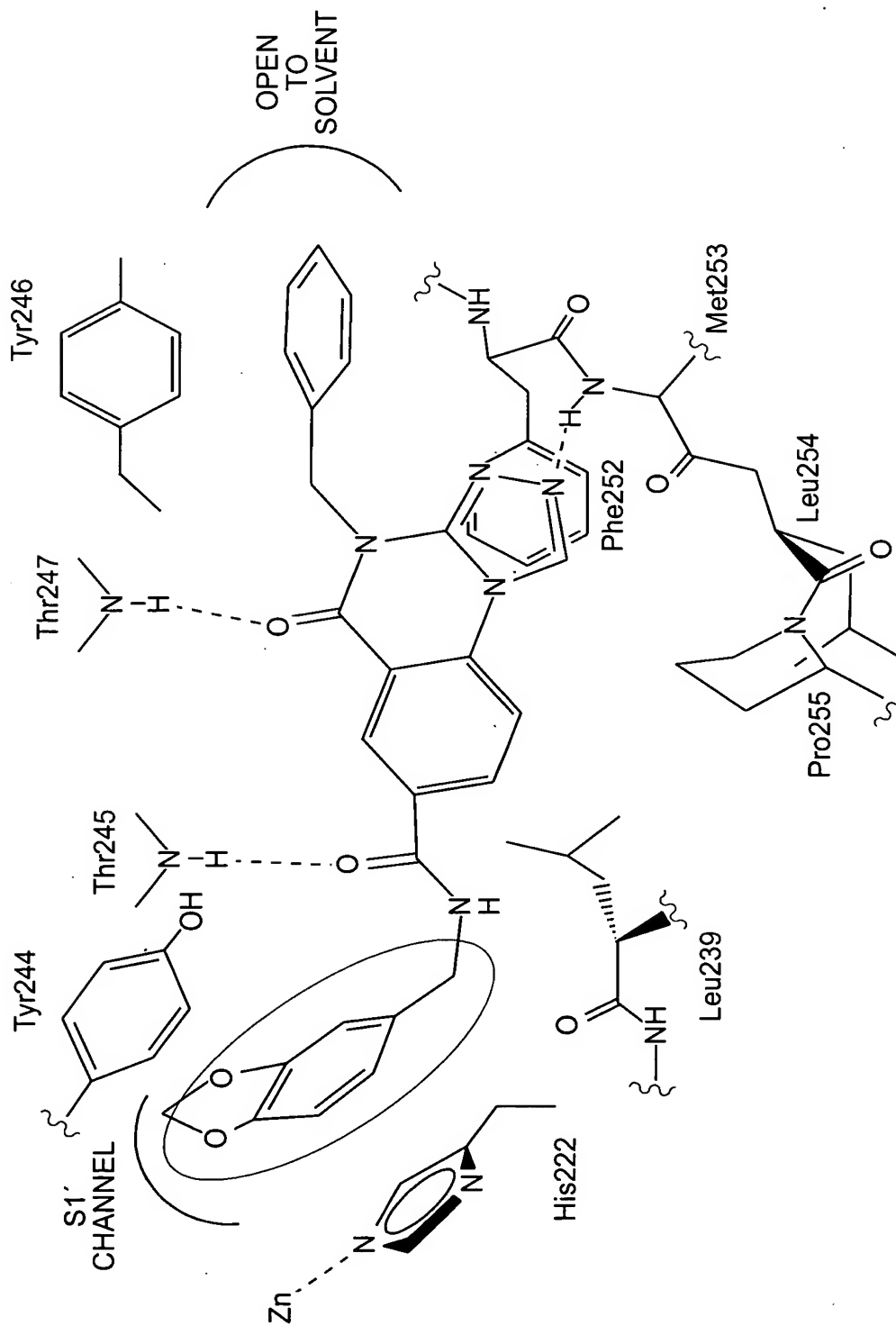
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FIG. 7 SYNTHESIS EXAMPLE 39 BINDING MODE

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FIG. 8 SYNTHESIS EXAMPLE 57 BINDING MODE



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FIG. 9. COORDONATES IN THE SPACE OF THE HYDROPHOBIC GROUPS AND HYDROGEN BOND ACCEPTORS OF THE PHARMACOPHORE

